Advanced symptoms are associated with myocardial damage in patients with severe aortic stenosis

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Einführung

Although there has been a decrease in cardiovascular disease mortality across higher income countries, huge inequalities persist with cardiovascular disease accounting for more than 50% of all deaths in many middle-income countries compared with less than 30% in the high-income countries of Western Europe [1]. Accounting valvular heart diseases (VHD) for a significant part of cardiovascular disease, after hypertension and coronary artery disease (CAD). In industrialized countries, the prevalence of valvular heart diseases is estimated at 2.5% and, because of the predominance of degenerative etiologies, the prevalence of valvular disease increases markedly after the age of 65 years [2], from 0.7% in 18-44 years of age to 13.3% in the 75 years and older groups [3]. Thus, with the ageing of the population and with the use of better diagnostic tools, calcific aortic stenosis (AS) has become the most common primary valve disease leading to surgery or catheter intervention in Europe and North America, with a growing prevalence in the general population [3]. In most European countries moderate aortic stenosis is present in 5% of the population over the age of 75 and severe AS in 3%.

Precise molecular mechanisms involved in the pathophysiology underlying calcific aortic stenosis are still lacking. As has been well described [4, 5], for the normal function of the aortic valve, the leaflets must be both strong and flexible to withstand the considerable mechanical stress and strain associated with valve function. The cusp microarchitecture is crucial and consists of three layers: fibrosa, spongiosa, and ventricularis. Valvular endothelial cells (VEC) are located at valvular surfaces, constituting a barrier that regulates valve permeability, the adhesion of inflammatory cells and paracrine and systemic signaling. Valvular interstitial cells (VIC), the major cell type, are present throughout all valvular layers. Valvular interstitial cells are key in valve remodeling,

regulating both the synthesis and degradation of extracellular matrix components. Physiologically, Valvular interstitial cells exist in a quiescent state, with similar characteristics to fibroblasts. Stimulation of VECs and VICs by molecular and mechanical triggers including high blood pressure, altered shear stress, cytokines, and growth factors contributes to aortic stenosis pathophysiology, altering the local valve environment and activating the calcification process. Indeed, nowadays calcific aortic valve stenosis is viewed as a fibrocalcific disease; triggered in areas of the valve with altered flow patterns, increased mechanical stress, and reduced shear stress, which causes endothelial damage and activation [4]. This initial phase shows similarities with atherosclerosis and shares common risk factors including age, male gender, body mass index, smoking, hypertension, and altered lipid metabolism [6]. During this initiation phase mechanical stress, endothelial damage, inflammation, and lipid deposition play the main role in calcific aortic stenosis pathophysiology. As mentioned, the first event is believed to be endothelial damage resulting from increased mechanical stress and reduced shear stress [7]. Shear stress is highest in the cusps adjacent to the coronary ostia because of the influence of coronary artery flow. Consequently, the non-coronary cusp has lower shear stress and is most frequently involved in aortic stenosis. Mechanical tissue stress is highest around the flexion areas of the cusps near their attachment to the aortic root, being a frequent region where aortic valve lesions are observed [8]. Endothelial disruption may allow inflammatory cells to penetrate the valvular endothelium activating forwarded steps of a cascade that favors the accumulation of lipids in these areas of inflammation, including low-density lipoprotein and lipoprotein(a), which undergo oxidative modification being then highly cytotoxic and capable of stimulating more inflammatory activity and subsequent mineralization [9, 10]. This initial pathophysiological phase of inflammation is supported by studies demonstrating increased systemic C-reactive protein concentrations, a marker of inflammation, in patients with aortic stenosis [11]. And more recently by noninvasive

imaging studies, which used the combination of positron emission tomography and computed tomography with Fluorine-18 fluorodeoxyglucose (18F-FDG) as a marker of macrophage activity. Increased 18F-FDG levels have been described in patients with aortic stenosis compared with controls, displaying a progressive rise in activity with increasing valve severity [12]. After this initial phase of inflammation and lipid deposition, in a second described pathophysiological phase of progressive valve narrowing, local fibrosis and calcification become overwhelming, ultimately leading to severe calcification and valvular dysfunction. The stenotic aortic valve is characterized by extensive thickening due to the accumulation of fibrous tissue and remodeling of the extracellular matrix. Abundant fibroblast-like cells are found in the aortic valve leaflets, and a subpopulation of these cells become activated during the inflammatory activity and differentiate into myofibroblasts, which are believed to play an important role in the accelerated fibrosis observed in aortic stenosis [13]. The renin-angiotensin system is thought to have the potential to modify this fibrotic process [14]. Finally, aortic valve calcification becomes crucial in the pathophysiology of aortic stenosis, leading to valve narrowing and stenosis. Disorders of mineral metabolism, including Paget disease, osteoporosis, vitamin D polymorphisms, and hemodialysis, are all associated with an increased prevalence of aortic stenosis. Interestingly, microscopic areas of calcification can be observed in the early stages of aortic sclerosis, co-localizing areas of inflammation and lipid deposition [15, 16]. This progression is thought to be driven by the differentiation of myofibroblasts into osteoblasts under the influence of different signaling pathways. Osteoblasts subsequently coordinate calcification as part of a complex process finally facilitating new bone formation [17]. Continued remodeling of these calcification areas occurs during the progress to severe calcific aortic stenosis [18]. Combined positron emission tomographic and computed tomographic imaging has confirmed the pathogenic role of calcification in aortic stenosis using 18F sodium fluoride. This tracer exchanges with hydroxyl groups on

hydroxyapatite crystal having the potential to detect areas of calcification under development and or remodeling. Uptake of 18F sodium fluoride is increased within stenotic aortic valves compared with control subjects, displaying a progressive rise in activity with increasing disease severity [12]. All these data add further support to calcification as an important process in the pathogenesis of aortic valve narrowing during this second propagation phase of the disease.

Thus, calcific aortic stenosis is a gradually progressive disease, characterized by a long asymptomatic period lasting several decades with inflammation and progressive fibro-calcification of the aortic valve, followed by a shorter symptomatic phase associated with severe or “critical” narrowing of the orifice of the aortic valve. Once symptoms occur, patient survival is markedly limited, expressing an end stage of the disease with sometimes even rapidly exponential progression from mild exertional to advanced heart failure symptoms.

Despite growing knowledge, experience, and technological developments, the only treatment for severe aortic stenosis is surgical or trans-catheter aortic valve replacement (AVR). In the last decade multiple observational pharmacological studies and randomized controlled trials acting in different pathophysiological pathways attempted to demonstrate a reduction of the progression to surgery of calcific aortic stenosis. Statins are widely used for lipid lowering in atherosclerosis, being a specific inhibitor of hydroxymethylglutarylcoenzyme A-reductase (HMG-CoA-reductase) with also anti-inflammatory effects. With the hypothesis of reduction of lipid deposition in the aortic valve leaflets and less VIC’s activation due to anti-inflammatory effects, retrospective studies suggested that statins might be of benefit in calcific aortic stenosis [19-23]. But, subsequent randomized controlled trials demonstrated that statins in fact have no significant effect on calcific aortic stenosis progression or in clinical outcomes [24].

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are well-known attenuators of the cascade renin–angiotensin-aldosterone, which has been associated with the fibrocalcific pathophysiological pathway of aortic stenosis [4]. In patients with calcific AS, one randomized trial has shown a modest but significant reduction of myocardial hypertrophy in patients treated with ramipril [25], and one clinical observational study has suggested that ACE inhibitors and ARBs are associated with favorable effects on symptoms (dyspnea and exercise tolerance) and improved survival [26]. But, although, some observational retrospective studies, investigating the effect of ACE inhibitor and ARBs on aortic stenosis progression, were associated with less valve fibrosis and calcification [27, 28], there is still conflicting data [23] and most importantly prospective randomized controlled trials are lacking on this topic. Thus, pharmacological interventions until now have failed to alter the course of calcific aortic stenosis.

Therefore, guidelines [29, 30] still advocate aortic valve replacement for patients with severe aortic stenosis in the presence of either: (A) classical symptoms (angina, syncope, or exertional dyspnea); or (B) left ventricular (LV) systolic dysfunction (i.e. LV ejection fraction <50%). Being the results of surgical AVR for acquired aortic stenosis a medical advantage of the last decades. Age-corrected survival after aortic valve replacement is excellent for patients over the age of 65 years and is similar to that of the normal population of that age [31]. In the absence of extracardiac co-morbidities and in the absence of coronary artery disease, aortic valve replacement can be performed at a 2% to 3% operative mortality with an 85% age-corrected 10-year survival. This excellent outcome can be attributed to a variety of factors including the universal use of intraoperative cardiac protection, the insertion of hemodynamically excellent and durable valve prostheses, but also a proper “timing” of aortic valve replacement. Nowadays, there is a clear acceptance or tendency to concentrate the diagnosis and management of

patients with valvular heart disease in high-specialized heart centres, being the main purpose of these heart valve centres as centres of excellence in the treatment of valvular heart disease to deliver better quality of care. This is achieved through greater volumes associated with specialization of training, continuing education and clinical interest. In this way, specialization will also result in timely referral of patients before “irreversible” adverse effects occur in patients with valvular heart disease conditions. Indeed, the presence of “advanced” heart failure *symptoms* in patients with aortic stenosis is associated with worse outcomes and also with persistence of symptoms after successful aortic valve replacement [32, 33], giving evidence of the participation of other factors rather than the solely presence of aortic valve narrowing. Being of crucial importance the identification of these factors, to avoid the referral of patients to aortic valve replacement with a predisposition to have worse postoperative outcomes and persistence of heart failure, which also means higher healthcare costs.

Classically, aortic stenosis has been seen as a solely progressive calcification of the aortic valve that causes a gradual reduction in valve area leading to a “critical stenosis”, which theoretically triggers the typical aortic stenosis related symptoms. As have been proposed the definition of “critical aortic stenosis” should be that valve area small enough to cause the symptoms of aortic stenosis: a “critical” situation predicting aortic valve replacement. But, this “critical aortic valve area” seems to be not a single fixed value but a continuous range [34], in fact, this “critical” zone varies from patient to patient. As Otto and colleagues [35] pointed out, patients who are symptomatic but have a valve area >1.0 cm^2 probably have symptoms based on another extravalvular problem. Patients with a valve area of <0.8 cm^2 who have typical symptoms almost certainly have them on the basis of aortic valve stenosis. And patients with areas ranging from 0.8 to 1.0 cm^2 are in the gray zone in which, again, a variety of other clinical factors must be playing a role. Today calcification is

no longer considered a passive consequence of ageing but an active process involving cellular and multiple molecular pathways. Dweck and colleges revived the concept of calcific aortic stenosis as a *disease of the valve and myocardium [7]*. Aortic stenosis causes an increase in pressure afterload and ventricular wall stress that stimulates hypertrophy of the left ventricular myocardium. Myocytes enlarge and wall thickness increases in a response that initially restores wall stress and preserves left ventricular function [36]. But, an inappropriately high left ventricular hypertrophy has been demonstrated to be associated with worse prognosis [37]. In calcific aortic stenosis, patients display a marked variation in the magnitude of their hypertrophic response. The mechanisms involved in left ventricular hypertrophy in patients with aortic stenosis should then be more than a simple response to mechanical forces, explaining the marked heterogeneity between symptom onset and the severity of valve narrowing that is observed (i.e. gray zone of aortic valve area between 0.8 and 1.0 cm^2). The resulting LV structural changes (i.e. progressive myocardial fibrosis and stiffness [38]) may gradually cause diastolic and, at a later stage, systolic dysfunction [39]. The precise mechanisms behind this transition from adaptive to maladaptive LV hypertrophy are poorly defined but involve myocardial damage and are not directly related with the severity of valve narrowing [40]. The maladaptive response of the LV involves programmed cell death or apoptosis's pathways and remodeling of the extracellular matrix with deposition of interstitial collagen, leading to myocardial fibrosis and increased myocardial wall stiffness [41]. These pathophysiological pathways seem to run parallel to the progression of the aortic valve disease, and are influenced from multiple factors explaining the heterogeneous response between two different patients with similar aortic stenosis severity. Several studies aimed to evaluate diagnostic methods for early detection of LV interstitial fibrosis in patients with aortic stenosis before any signs of impaired cardiac function become apparent. Echocardiography's studies evaluated the longitudinal LV function by measuring the global

longitudinal peak systolic strain (speckle tracking) or the mitral annular plane systolic excursion (M-mode). They were able to demonstrate LV myocardial involvement despite preserved LV ejection fraction, and also were predictors of symptoms onset in patients with asymptomatic aortic stenosis. Using T1 mapping techniques, with histology validated cardiac magnetic resonance studies detected diffuse myocardial fibrosis even after extended focal fibrosis was present, and also showed prognostic significance, but still there seems to be a huge overlap when compared with elderly population without aortic valve disease. And finally there are several biomarkers of myocardial fibrosis pathway's activity under investigation (transforming growth factor β1, collagen-derived peptides, matrix metalloproteinases, micro RNAs, etc) [42]. Anyhow, a disproportionate or more marked LV remodeling in patients with aortic stenosis may clinically translate into onset of advanced symptoms and increased risk for potential permanent left ventricle dysfunction and adverse cardiovascular events.

Indeed, not only parameters expressing a valve narrowing (i.e. valve area, peak velocity, and gradients) but also those associated with involvement of the left ventricle (i.e. left ventricle ejection fraction, hypertrophy, reduced LV global longitudinal peak systolic strain, etc.) have been associated with the development of symptoms in the course of aortic stenosis progression. Thus, it can be argued, that once aortic stenosis is severe, the "onset" of symptoms and more importantly the severity of them depend on a combination of aortic valve narrowing with multiple other linked factors, such as the association with comorbidities (i.e. hypertension, diabetes, coronary artery disease, etc.), age, male gender, and left ventricle myocardial remodeling.

Moreover, it has been demonstrated that the cardiac structural and functional alterations are associated not only with the development of symptoms [43, 44], but also with the type of symptom (i.e. angina, dyspnea, or syncope) [45, 46]. Patients with syncope displayed

smaller left ventricle dimension, stroke volume, and left atrial volume index, and patients with dyspnea had the worst diastolic function with largest left atrial volume index and highest E/e' ratio; while having a similar aortic valve area and gradient.

However, it has never been investigated which clinical and echocardiographic characteristics are associated with the presence of "advanced" symptoms in patients with severe aortic stenosis referred for aortic valve replacement. It remains to be determined, whether advanced symptoms in patients with severe aortic stenosis are associated solely with aortic valve narrowing or also with other factors. It is more likely that multiple factors are playing a role in the pathogenesis of severe aortic stenosis. There are endless possible pathways influencing and or aggravating the afterload imposed on left ventricle by an aortic valve narrowing. For instance a more pronounced local inflammatory response, which could disseminate systemically through paracrine and systemic signaling activating fibrosis and apoptosis pathways in distal areas leading to earlier and more pronounced myocardial damage. Phenomenon that may get enhanced in association with comorbidities, triggering heart failure symptoms in an earlier phase of aortic valve calcification and narrowing with valve areas in the gray zone of 0.8 to 1.0 cm^2.

Hence, we aimed to describe the relationship between the presence of "advanced" symptoms and the clinical and echocardiographic characteristics of a cohort of patients with severe aortic stenosis referred for aortic valve replacement. Biomarkers of inflammation (C-reactive protein), of cardiovascular stress (NT-pro-B-type natriuretic peptide), and of myocardial damage (high-sensitivity cardiac troponin T) were also evaluated.

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Original article

Advanced symptoms are associated with myocardial damage in patients with severe aortic stenosis

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ABSTRACT

Background: Once aortic stenosis (AS) is severe, patients develop symptoms at different stages. Indeed, symptom status may correlate poorly with the grade of valve narrowing. Multiple pathophysiological mechanisms, other than valvular load, may explain the link between AS and symptom severity. We aimed to describe the relationship between the severity of symptoms and the characteristics of a cohort of patients with severe AS already referred for aortic valve replacement (AVR).

Methods: We analyzed 118 consecutive patients (70 ± 9 years, 55% men) with severe AS referred for AVR. We identified 84 patients with New York Heart Association (NYHA) I–II, and 34 with NYHA III–IV symptoms. Clinical and echocardiographic parameters were compared between these two groups. Left ventricular ejection fraction (LVEF), global longitudinal peak systolic strain (GLPS), NT-pro-B-type natriuretic peptide (BNP), and high-sensitive troponin T (hs-TNT) were determined at the time of admission.

Results: AS severity was similar between groups. Compared with the NYHA I–II group, patients in NYHA III–IV group were older and more likely to have comorbidities, worse intracardiac hemodynamics and more LV damage. Variables independently associated with NYHA III–IV symptomatology were the absence of sinus rhythm, higher E/e′ ratio, and increased hs-TNT. GLPS showed a good correlation not only with hs-TNT as a marker of myocardial damage, but also with markers of increased afterload imposed on LV, being not directly related with advanced symptoms.

Conclusions: Advanced symptoms in patients with severe AS referred for AVR are associated with worse intracardiac hemodynamics, absence of sinus rhythm, and more myocardial damage. It supports the concept of transition from adaptive LV remodeling to myocyte death as an important determinant of symptoms of heart failure.

Introduction

Aortic stenosis (AS) is a progressive disease characterized by a long asymptomatic period. Once symptoms occur, patient survival is markedly limited. Progressive pressure overload imposed on the left ventricle (LV) in the presence of longstanding AS often leads to LV remodeling and hypertrophy, even in the absence of symptoms [1]. These structural changes may gradually cause diastolic and, at a later stage, systolic dysfunctions [2]. Furthermore, it has been demonstrated that the cardiac structural and functional alterations are associated not only with the development of symptoms [3,4], but also with the type of symptom (i.e. angina, dyspnea, or syncope) [5,6]. However, it has been never investigated which clinical and echocardiographic characteristics are associated with the presence of advanced symptoms in patients with severe AS referred for aortic valve replacement (AVR). Whether the severity of valve narrowing itself or the cardiac structural changes secondary to valvular afterload determines the severity of symptoms is still not well understood. Hence, we aimed to describe the relationship between the presence of advanced symptoms and the clinical and echocardiographic characteristics of a cohort of patients with severe AS referred for AVR.

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Methods

Population

Between August 2012 and February 2013, 118 patients (70 ± 9 years, 55% men) referred to our center with severe AS for AVR were evaluated by our echocardiographic laboratory and prospectively enrolled in this study. Severe AS was the principal indication for surgery, and patients having an associated cardiac valve lesion more than moderate were excluded. Symptoms related to AS were recorded by a cardiologist at admission and before echocardiographic evaluation. According to a combination of the Canadian Cardiovascular Society score (CCS) and the New York Heart Association (NYHA) functional class, the symptoms were represented as follows: NYHA-I, no symptoms; NYHA-II, symptoms with moderate exertion (including CCS II and I); NYHA-III, symptoms with mild exertion (CCS III); and NYHA-IV, symptoms at rest (CCS IV). Patients presenting an isolated episode of syncope with moderate exertion without other symptoms in daily activity were considered to be at NYHA class II. Afterwards, the whole population was divided into two groups: 84 with NYHA I–II and 34 with NYHA III–IV (advanced) symptoms. Within patients in NYHA-I class, the indication for surgery was assessed by the referring cardiologist, usually by an abnormal exercise test or the rate of peak transvalvular velocity progression. Other data collected at the time of admission included the cardiovascular risk factors, previous history of renal injury (diagnosed chronic renal failure, history of even mild acute renal injury in the last 6 months, or rise in the preoperative serum creatinine), stroke or transient ischemic attack, presence of coronary artery disease (CAD: stenosis >50% on angiography), N-terminal-pro-B-type natriuretic peptide (BNP), C-reactive protein (CRP), and high-sensitive troponin T (hs-TNT). The BNP ratio (the ratio of BNP to the reference BNP value for age and sex) was also measured. BNP ratio >1 was interpreted as clinical BNP activation as already suggested [7]. Finally, absence of sinus rhythm was defined as history of permanent or persistent atrial fibrillation (AF), or presence of AF at the time of submission.

Echocardiographic study

Commercially available ultrasound machines (Vivid-7 and E9, General Electric Healthcare, Wauwatosa, WI, USA) equipped with an M4S or M5S probe were used for all echocardiographic examinations. For LV and left atrial (LA) chamber quantification, we followed the recommendations [8]. LA volume (LAV) was obtained with the biplane area-length technique, and LA area (LAA) was measured in an apical four-chamber view. LV volumes and ejection fraction (EF) were calculated using the biplane Simpson disk method. LV mass was estimated using the linear method with the formula recommended by the American Society of Echocardiography [9]. Continuous wave Doppler was used to measure the aortic transvalvular peak velocities; peak and mean gradients were calculated using the simplified Bernoulli equation, and aortic valve area (AVA) using the continuity equation. AS severity was graded according to recommended guidelines [10]. Peak velocities during early diastole (e′) were obtained at the level of septal mitral annulus using pulsed wave tissue Doppler. The E/e′ ratio was then calculated. Mitral annular plane systolic excursion (MAPSE) was measured in an apical four-chamber view with M-mode beam positioned on the lateral mitral annulus. In patients with AF, measurements were averaged from five heart cycles.

Left ventricular strain

Using the two-dimensional speckle-tracking approach, the global longitudinal myocardial deformation was evaluated as the average of the segment strains from the apical four-chamber, two-chamber, and long-axis views. Endocardial borders were traced with a software tool (AFI: Automated Function Imaging, GE Healthcare) that automates 2D speckle tracking to measure real-time deformation of the myocardial wall. After the tracking quality was verified for each segment, myocardial motion was analyzed by speckle tracking within the region of interest [11]. In patients with AF, we recorded apical loops with similar R–R intervals. When not possible, global longitudinal peak systolic strain (GLPS) was recorded as missed.

GLPS could be successfully measured in 114 of 118 patients (97%). Additionally, intraobserver and interobserver variability was assessed in 20 patients. The intraobserver analysis showed a mean absolute difference of 0.1% (95% confidence interval, −0.18 to 0.39%) for GLPS. The interobserver analysis showed a mean absolute difference of −0.55% (95% CI, −0.98 to −0.12%) for GLPS, with good intraclass correlation (0.99, 95% CI 0.96–0.99; $p < 0.001$).

Statistical analysis

Continuous variables are expressed as mean ± SD. Dichotomous data are presented as percentages. Statistical differences between groups were assessed using Student's *t*-test for continuous variables or Fisher's exact test for categorical variables. Multigroup comparisons of continuous variables were performed using an analysis of variance. Continuous data that were not normally distributed (i.e. BNP, hs-TNT, CRP, and EuroSCORE) are presented as median values and corresponding interquartile ranges (IQR: 25th and 75th percentiles), and were analyzed using non-parametric statistical tests, as the Mann–Whitney test, and their natural logarithms were used for logistic regression and correlation. Variables associated with more advanced symptoms were determined with binary logistic regression analyses. Those with a good correlation and assumed to have a clinical implication (i.e. age, diabetes, hypertension, and CAD) were incorporated into the model and selected by a backward procedure. Two-tailed *p*-values <0.05 were considered statistically significant. Analyses were performed using SPSS software (IBM-SPSS Statistics, Version 20, IBM Corp., New York, NY, USA).

The study was conducted in accordance with the Declaration of Helsinki and was approved by the local research ethics committee.

Results

Characteristics of the patients

Tables 1 and 2 list the demographic and echocardiographic characteristics of the study population. In the whole cohort, 16% ($n = 19$) of patients were characterized as being in NYHA class I, and all other patients were symptomatic as follows: 55% ($n = 65$) in NYHA class II, 26% ($n = 31$) in NYHA class III, and 2.5% ($n = 3$) in NYHA class IV. A bicuspid aortic valve was observed in 20 patients (17%). From the total population, 87 patients (74%) had no or mild mitral valve regurgitation (MR), and 31 (26%) had mild to moderate MR. The median overall logistic EuroSCORE was 3.7 (IQR: 1.95–6.5). The indexed AVA was 0.37 ± 0.09 cm^2/m^2 and LVEF 58 ± 10%.

Surgical characteristics

A total of 68 (57.6%) patients underwent isolated AVR. A biological prosthesis was inserted in 93% of patients. A coronary artery bypass graft (CABG) was performed in 21 patients (17.8%) with no differences between groups. Interestingly, of the 54 patients presenting with chest pain (angina), only 13 (24%) had a CAD on angiography, and 12 (22%) received a revascularization (one patient underwent a surgical AVR with one vessel CAD considered to be non-revascularizable). A higher rate of concomitant pulmonary vein

Table 1
Patient characteristics.

	Total (n = 118)	NYHA I–II (n = 84)	NYHA III–IV (n = 34)	p-Value
Age, years, mean ± SD	70 ± 9	69 ± 8.8	73 ± 9.5	**0.03**
Male, n (%)	65 (55)	46 (55)	19 (56)	0.91
Symptoms, n (%)				
Chest pain	54 (46)	35 (42)	19 (56)	0.16
Syncope	20 (17)	15 (18)	5 (15)	0.68
Dyspnea	91 (77)	58 (69)	33 (97)	**0.001**
Comorbidities, n (%)				
Hypertension	101 (86)	68 (81)	33 (97)	**0.02**
Diabetes	26 (22)	14 (17)	12 (35)	**0.03**
Dyslipidemia	59 (50)	37 (44)	22 (65)	**0.04**
Smoker	23 (19.5)	18 (21)	5 (15)	0.46
Atrial fibrillation	10 (8.5)	2 (2.4)	8 (23.5)	**0.001**
Coronary artery disease[a]	27 (23)	12 (14)	15 (44)	**0.001**
Previous cerebral infarction	8 (6.8)	5 (6)	3 (9)	0.69
Previous renal injury	20 (17)	8 (9.5)	12 (35)	**0.001**
Chronic obstructive pulmonary disease	14 (12)	10 (12)	4 (12)	1.0
Log EuroSCORE, median (IQR)	3.7 (1.95–6.5)	3 (1.72–5.9)	4.8 (3.4–12)	**0.002**
Treatment, n (%)				
Aspirin	63 (53.4)	46 (55)	17 (50)	0.64
Beta-blockers	64 (54)	40 (48)	24 (71)	**0.02**
ACE-inhibitors	39 (33)	27 (32)	12 (35)	0.74
ARB	29 (25)	20 (24)	9 (26.5)	0.76
Statins	62 (52.5)	39 (46)	23 (68)	**0.04**
Diuretics	50 (42.5)	26 (31)	24 (71)	**<0.001**

NYHA, New York Heart Association functional class; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.
Bold values identify a p.
[a] Coronary stenosis >50% in at least one territory, as depicted by preoperative coronary angiography.

isolation (21 vs. 7%, p = 0.05) was performed in the NYHA III–IV group. Moreover, a trans-catheter aortic valve implantation (TAVI) was also more frequently performed in this group (18 vs. 3.5%, p = 0.02).

The overall in-hospital mortality was 1.7% (2 of 118 patients), and tended to be higher in the NYHA III–IV group (5.9% vs. 0%; p = 0.08).

Functional class and baseline characteristics

Patients with NYHA III–IV were significantly older than NYHA I–II patients and more likely to have comorbidities such as hypertension, renal injury, dyslipidemia, diabetes, atrial fibrillation, and CAD. In addition, NYHA III–IV patients had a higher EuroSCORE and were more likely to be receiving beta-blockers, statins, and diuretics.

Table 2
Laboratory and echocardiographic indices.

	Total (n = 118)	NYHA I–II (n = 84)	NYHA III–IV (n = 34)	p-Value
Echocardiographic indices				
EF, %	58 ± 10.2	60 ± 8.3	52 ± 12.4	**<0.001**
E/e′	16 ± 6.3	14.2 ± 5	20.6 ± 6.7	**<0.001**
MAPSE, mm	14.4 ± 3.4	15.1 ± 3.2	12.6 ± 3.4	**<0.001**
GLPS, %	−15.4 ± 3.8	−16.4 ± 3	−13 ± 4	**<0.001**
Stroke volume index, ml/m^2	36.9 ± 10	39.2 ± 9.7	31.5 ± 8.9	**<0.001**
EDVi, ml/m^2	43.3 ± 17.5	41.7 ± 16	47 ± 20.3	0.17
ESVi, ml/m^2	18.7 ± 11.8	17 ± 9.8	22 ± 15.1	**0.04**
LAVi, ml/m^2	45 ± 14.6	42.5 ± 13	51.2 ± 17	**0.003**
LAAi, cm^2/m^2	12.3 ± 2.8	11.8 ± 2.6	13.6 ± 2.9	**0.001**
Aortic valve area, cm^2	0.7 ± 0.16	0.7 ± 0.16	0.66 ± 0.17	0.15
Aortic valve area index, cm^2/m^2	0.37 ± 0.09	0.37 ± 0.09	0.35 ± 0.08	0.22
Peak aortic velocity, m/s	4.3 ± 0.7	4.35 ± 0.6	4.05 ± 0.9	**0.045**
Mean aortic pressure gradient, mmHg	50.2 ± 16	51 ± 13.5	47.4 ± 21	0.23
Trans-tricuspidal gradient, mmHg	34.5 ± 11	31.3 ± 6.6	41 ± 14.7	**<0.001**
Mass index, g/m^2	145 ± 42.7	143 ± 38	148 ± 50	0.52
Posterior wall diastolic thickness, mm	13 ± 2	12.8 ± 2	13.4 ± 2.4	0.15
Zva, mmHg/ml m^2	5.9 ± 1.7	5.6 ± 1.4	6.5 ± 2.2	**0.01**
Laboratory parameters				
BNP, ng/L, median (IQR)	559 (278–1654)	399 (215–1074)	1512 (677–6179)	**<0.001**
Activated BNP, n (%)	81 (68.6)	52 (61.9)	29 (85.3)	**0.016**
hs-TNT, ng/L, median (IQR)	12 (9–18)	11 (8–16)	20 (10–59.5)	**<0.001**
Positive hs-TNT, n (%)	49 (41.5)	29 (34.5)	20 (58.8)	**0.02**
CRP, mg/dl, median (IQR)	0.2 (0.1–0.3)	0.2 (0.1–0.2)	0.35 (0.18–0.9)	**0.001**
Creatinine, mg/dl	1.0 ± 0.34	0.95 ± 0.3	1.14 ± 0.4	**0.003**
Glucose, mg/dl	119 ± 39	117 ± 33	124 ± 51	0.36

NYHA, New York Heart Association functional class; EF, left ventricular ejection fraction; E/e′, E/e′ ratio from the medial mitral annulus; MAPSE, mitral annular plane systolic excursion; GLPS, global longitudinal peak systolic strain; EDVi, LV end-diastolic volume index; ESVi, LV end-systolic volume index; LAVi, left atrial volume index; LAAi, left atrial area index; Zva, valvulo-arterial impedance; BNP, pro-B-type natriuretic peptide; Activated BNP, BNP ratio >1; hs-TNT, high-sensitive troponin T; Positive hs-TNT, TNT >14 ng/L; CRP, C-reactive protein. Unless otherwise specified, values are expressed as mean ± SD.
Bold values identify a p.

Table 3
Correlations with advanced NYHA functional class.

Age	0.203	0.03
Male	0.01	0.91
Hypertension	0.208	0.02
Diabetes	0.204	0.03
Smoker	−0.077	0.41
History of renal injury	**0.311**	**0.001**
Dyslipidemia	0.187	0.04
Coronary artery disease	0.201	0.03
Sinus rhythm	**−0.344**	**<0.001**
Beta-blockers	0.209	0.02
ACE-inhibitors	0.030	0.74
Diuretics	**0.363**	**<0.001**
log BNP[a]	**0.459**	**<0.001**
BNP ratio[§]	**0.392**	**<0.001**
log hs-TNT[a]	**0.461**	**<0.001**
log CRP[a]	0.270	0.004
Hematocrit	−0.227	0.02
Creatinine	0.269	0.003
Log EuroSCORE	**0.338**	**<0.001**
Peak aortic velocity	−0.186	0.045
Mean aortic pressure gradient	−0.111	0.23
Aortic valve area	−0.135	0.15
Valvulo-arterial impedance (Zva)	0.232	0.01
Trans-tricuspidal gradient	**0.419**	**<0.001**
LAAi	**0.305**	**0.001**
LAVi	0.272	0.003
LV mass index	0.059	0.52
ESVi	0.193	0.04
EDVi	0.139	0.13
Stroke volume	**−0.361**	**<0.001**
LVEF	**−0.339**	**<0.001**
GLPS	**0.403**	**<0.001**
E/e′ ratio	**0.464**	**<0.001**
MAPSE	**−0.329**	**<0.001**

ACE, angiotensin-converting enzyme; BNP, B-type natriuretic peptide; hs-TNT, high-sensitive troponin T; CRP, C-reactive protein; LAAi, left atrial area index; LAVi, left atrial volume index; LV, left ventricular; ESVi, LV end-systolic volume index; EDVi, LV end-diastolic volume index; LVEF, left ventricular ejection fraction; GLPS, global longitudinal peak systolic strain; E/e′, E/e′ ratio from the medial mitral annulus; MAPSE, mitral annular plane systolic excursion.
Bold values identify a correlation coefficient >0.300.
[a] Natural logarithm; *r* Pearson ([§] or Spearman) correlation coefficient.

Interestingly, both patient groups had similar AS severity, but those with NYHA III–IV had a higher valvulo-arterial load (Zva) with worse hemodynamics (i.e. higher E/e′ ratio, pulmonary artery pressure, and LA dimensions) and worse LVEF and GLPS values. In addition, NYHA III–IV patients had significantly higher creatinine, BNP, and hs-TNT levels. Table 3 shows the correlations with advanced NYHA class, and Table 4 the multivariable logistic regression analysis, revealing that absence of sinus rhythm, E/e′ ratio, and hs-TNT were risk-adjusted variables associated with more advanced symptoms, even after adjustment for CAD.

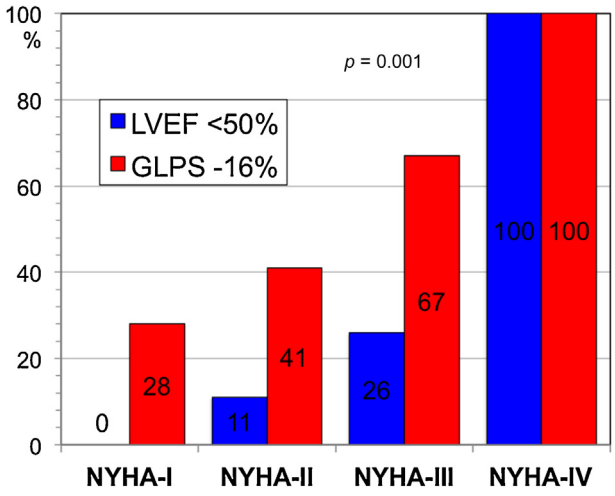

Fig. 1. Patients with severe aortic stenosis referred for surgery. Association between left ventricular damage, as assessed by GLPS worse than −16% and ejection fraction <50%, and NYHA functional class. GLPS, global longitudinal peak systolic strain; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Left ventricular function, biomarkers and NYHA functional class

In the whole population, there were three times more patients with LV involvement detected by GLPS (GLPS worse than −16%) than by using the classical LVEF definition of LV dysfunction (i.e. LVEF <50%). The difference was more pronounced in the NYHA I–II group (Fig. 1). Of the 114 patients with available GLPS and LVEF measurements, 96 (84.2%) had a normal LVEF. Interestingly, almost 40% (38 of 96) of these patients already had a reduced GLPS.

Patients with advanced symptoms had worse LVEF and GLPS values, and higher biomarker levels. Although the differences in the above variables did not reach statistical significance for most comparisons of NYHA I vs. II patients, the differences between NYHA class I and classes III and IV, or between NYHA class II and classes III and IV were significant in the majority. The indexed AVA

Table 4
Variables associated with NYHA III–IV functional class.

Variables	Univariate		Multivariable analysis	
	Odds ratio (95% CI)	*p*-Value	Odds ratio (95% CI)	*p*-Value
Age	1.06 (1.05–1.10)	0.031	–	–
Male sex	0.96 (0.43–2.13)	0.913	–	–
Diabetes mellitus	0.37 (0.15–0.90)	0.045	–	–
Hypertension	0.13 (0.02–1.01)	0.051	–	–
Coronary artery disease	0.21 (0.09–0.53)	0.001	–	–
Lack of sinus rhythm	12.6 (2.52–63.18)	0.002	**11.49 (1.90–69.6)**	**0.008**
LVEF	0.93 (0.89–0.97)	0.001	–	–
Peak aortic velocity	0.56 (0.31–0.99)	0.048	–	–
GLPS	1.30 (1.14–1.48)	<0.001	–	–
E/e′ ratio	1.19 (1.10–1.29)	<0.001	**1.15 (1.05–1.25)**	**0.002**
Preoperative MR	0.25 (0.10–0.59)	0.002	–	–
log TNT[a]	23.0 (4.99–105.9)	<0.001	**12.56 (2.70–58.5)**	**0.001**
log BNP[a]	8.5 (3.2–22.58)	<0.001	–	–
Creatinine	5.98 (1.52–23.43)	0.010	–	–

NYHA, New York Heart Association functional class; EF, left ventricular ejection fraction; GLPS, global longitudinal peak systolic strain; E/e′, E/e′ ratio from the medial mitral annulus; TNT, troponin T; BNP, B-type natriuretic peptide.
Bold values identify a *p*.
[a] Natural logarithm. MR, presence of mild to moderate mitral valve regurgitation (more than moderate MR was an exclusion criteria).

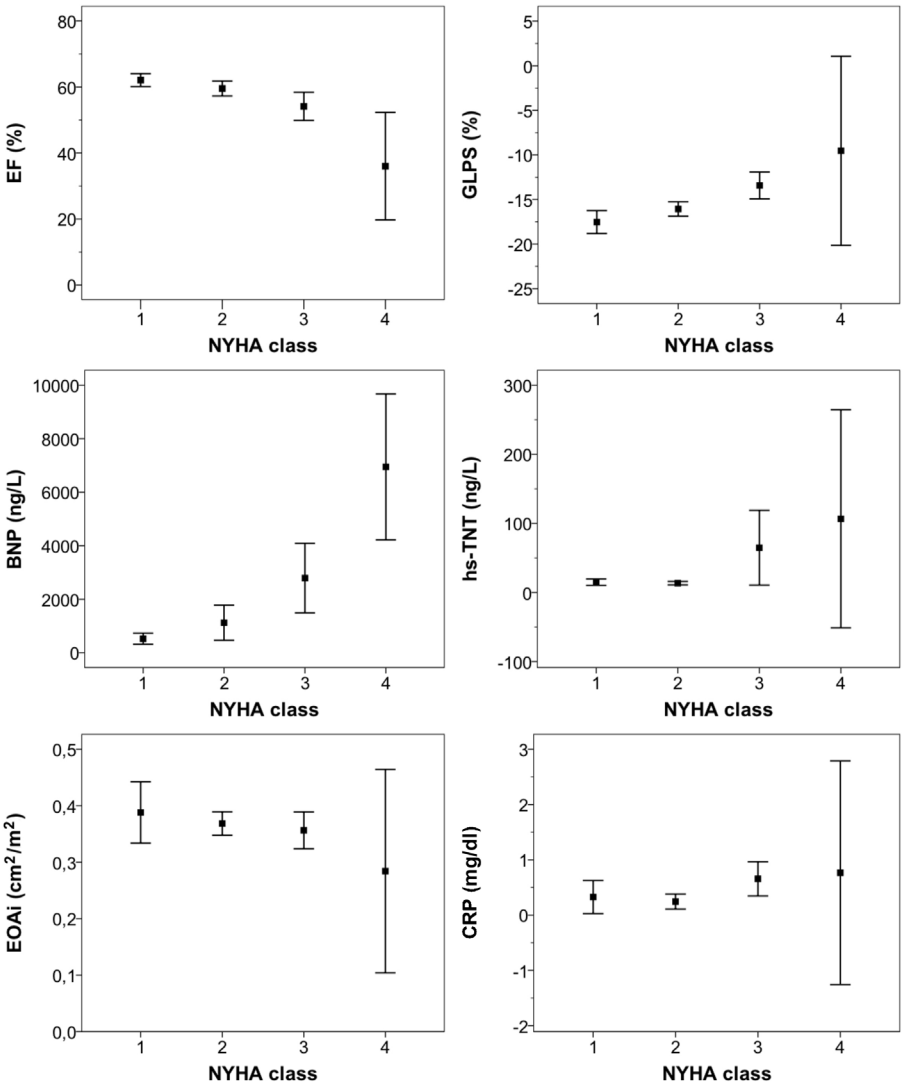

Fig. 2. Severe aortic stenosis. Association between NYHA functional class and left ventricular function, biomarkers, and aortic valve area (values are mean ± 95% CI). BNP, B-type natriuretic peptide; CRP, C-reactive protein; EF, ejection fraction; EOAi, aortic valve effective orifice area index; GLPS, global longitudinal peak systolic strain; hs-TNT, high-sensitive troponin T; NYHA, New York Heart Association.

tended to decrease with NYHA class, but did not reach statistical significance (Fig. 2 and Table 5).

GLPS correlations

GLPS showed a good correlation with other echocardiographic parameters of LV contractility or systolic function: LVEF ($r = -0.64$, $p < 0.001$), MAPSE ($r = -0.46$, $p < 0.001$), and indexed stroke volume ($r = -0.49$, $p < 0.001$); with parameters of left chambers dilatation: LV end-diastolic volume index ($r = 0.40$, $p < 0.001$), LV end-systolic volume index ($r = 0.59$, $p < 0.001$), and LA-volume ($r = 0.44$, $p < 0.001$); and moderately with LV hypertrophy: LV mass ($r = 0.32$, $p = 0.001$); and with parameters related with LV overload: indexed AVA ($r = -0.31$, $p = 0.001$) and Zva ($r = 0.35$,

Table 5
Left ventricular function, biomarkers, and AS severity in relation with NYHA.

	NYHA I[§]	NYHA II[#]	NYHA III[Ŧ]	NYHA IV[@]	*p*-Value
EF	62 ± 4[Ŧ@]	59.5 ± 9[@]	54 ± 11.5[§@]	36 ± 6.5[§#Ŧ]	**<0.001**
GLPS	−17.5 ± 2.5[Ŧ@]	−16 ± 3[Ŧ@]	−13.5 ± 4[§#]	−9.5 ± 4[§#]	**<0.001**
BNP	379 (215–633)[Ŧ@]	399 (240–1214)[Ŧ@]	1044 (662–2999)[§#]	6667 (6342–7413)[§#]	**<0.001**
BNP ratio	1.79 (0.97–2.61)[@]	3.73 (1.24–6.21)[@]	8.68 (3.19–14.18)	23.14 (9.07–37.21)[§#]	**0.002**
hs-TNT	14 (8.5–18)	11 (8–15)[Ŧ]	17 (10–55)[#]	125 (80.5–142)	**0.004**
CRP	0.2 (0.1–0.2)	0.1 (0.1–0.2)[Ŧ]	0.3 (0.1–0.9)[#]	0.4 (0.3–1.05)	**0.028**
EAOi	0.39 ± 0.11	0.37 ± 0.08	0.37 ± 0.09	0.28 ± 0.07	0.27

AS, aortic stenosis; EOAi, aortic valve effective orifice area index (cm^2/m^2); BNP, pro-B-type natriuretic peptide; BNP ratio, ratio of BNP value to normal BNP range according age and sex; NYHA, New York Heart Association functional class; EF, left ventricular ejection fraction; GLPS, global longitudinal peak systolic strain; hs-TNT, high-sensitive troponin T; CRP, C reactive protein. BNP, BNP ratio, hs-TNT, and CRP are medians (IQR). Differences reached statistical significance with: § group "NYHA I", # group "NYHA II", Ŧ group "NYHA III", and @ group "NYHA IV".
Bold values identify a *p*.

$p < 0.001$), but no significant correlation was found with transvalvular velocities or gradients. Hemodynamic parameters were also correlated with GLPS: E/e′ ratio ($r = 0.46$, $p < 0.001$) and trans-tricuspidal gradient ($r = 0.49$, $p < 0.001$). Finally, GLPS showed a good correlation with hs-TNT ($r = 0.42$, $p < 0.001$) and BNP ($r = 0.54$, $p < 0.001$).

Discussion

Our study shows the following in patients with severe AS referred for AVR: (1) advanced symptoms at the time of admission are not associated with the severity of the AS itself (grade of valve narrowing), but rather with age, comorbidities, worse intracardiac hemodynamics, and more LV damage. Variables independently associated with NYHA III–IV symptoms are the absence of sinus rhythm, higher E/e′ ratio, and increased hs-TNT; (2) GLPS showed a good correlation not only with markers of myocardial damage, but also with markers of increased afterload imposed on LV, being not independently related to advanced symptoms.

Degenerative AS [2,12] could be viewed as a disease with a silent phase of sclerosis and calcification of the valve, followed by progression of AS severity with different grades of LV involvement (LV overload, remodeling, and later myocardial damage). Once the AS is classified as severe, patients develop symptoms at different stages of the disease process. Indeed, within the severe AS category, symptom status may correlate poorly with the grade of valve narrowing [6]. Multiple pathophysiological mechanisms, rather than isolated valvular load, may therefore explain the link between AS and symptom severity.

We showed that advanced symptoms were not related to the grade of valve narrowing, but with more LV damage and worse intracardiac hemodynamics (i.e. E/e′ ratio). Our findings are in accordance with the results published by Park and colleagues [5], which demonstrated that symptomatic severe AS patients had lower cardiac output and higher E/e′ ratio while having a similar AVA and gradients, when compared to asymptomatic severe AS patients. Recently, Dahl and colleagues [4] reported that, despite similar AVA, development of symptoms in severe AS with *normal* LV function is associated with concentric remodeling, LV hypertrophy, impaired diastolic function, and LA dilatation but, interestingly, not with E/e′ ratio. These results probably reflect that patients in an earlier stage of AS – with normal LV systolic but already altered diastolic function – may have normal LV filling pressures at rest with only intermittent increases during exercise leading to LA dilatation and symptoms on maximal exertion [13].

Additionally, we found that the absence of sinus rhythm was independently associated with NYHA III–IV, reflecting the relationship between increased LV filling pressures, LA remodeling and dysfunction, with a higher rate of atrial fibrillation, which finally aggravates the symptoms [14].

We were unable to demonstrate a relationship between GLPS and severity of symptoms in our multivariable analysis. The groups of Takeda [15] and Tongue [3] have previously demonstrated that the long-axis excursion of the LV wall, irrespective of LVEF, is associated with symptom status in AS. Lancellotti et al. [16] studied asymptomatic patients with moderate to severe AS and also found that GLPS worse than −15.9% was a significant predictor of a combined end point of symptom development, AVR, or death. Our results and those of previous studies most likely reflect that GLPS is related with the development of symptoms, but not with the severity of them, where myocardial loss and worse intracardiac hemodynamics may play a more important role, which is also shown to be associated with adverse outcomes [17,18]. Indeed, GLPS is influenced not only by myocyte contraction, but also by the composition of the surrounding tissue (i.e. myocardial fibrosis) and pressure-volume characteristics of the LV [19,20]. In accordance with this, GLPS showed in our study a good correlation with different parameters, which are not only markers of myocardial damage, but also markers of increased afterload imposed on LV. This suggests that GLPS could be capable to detect an earlier stage of AS with LV involvement only secondary to pressure overload with or without mild diffuse subendocardial fibrosis, but before advanced myocardial injury and heart failure symptoms occur. Moreover, analyses of multidirectional strain suggested a progression from subendocardial (i.e. longitudinal strain) to transmural (i.e. circumferential and eventually radial strain) impairment of myocardial function in AS patients [21]. In the current study, 40% of patients with normal LVEF already had LV involvement, defined as a GLPS worse than −16%. Interestingly, the majority of these patients were in the NYHA I–II group (26 of 38; 68.5%), which could be explained maybe because in the NYHA III–IV group the LV circumferential and radial function involvement could already be detected by a reduced LVEF (i.e. <50%).

Finally, a positive relationship with more advanced NYHA functional class was showed for BNP levels and ratio (Table 3 and Fig. 2), but surprisingly, we did not find an independent association. Previous studies showed that natriuretic peptides correlate with the severity of AS [22], and symptomatic patients have significantly higher levels of BNP than asymptomatic patients with severe AS. In addition, in this latter group, the BNP levels are associated with the onset of symptoms [23]. But an overlap of plasma levels of BNP is observed in patients with NYHA classes I and II. In our population, we did not find differences between NYHA-I and NYHA-II groups respective BNP levels. Moreover, in a recent large prospective study, almost 60% of asymptomatic patients with isolated severe AS and normal LVEF had already a clinical BNP activation [7]. It could be argued that BNP is a sensitive marker with elevations also in earlier stages of the AS with only LV diastolic dysfunction and no or minimal symptoms. Later, a subsequent release of BNP is joined with the occurrence of myocardial damage, LV systolic dysfunction, and advanced symptoms. Indeed, BNP levels have been correlated to myocardial fibrosis and its surrogate markers (i.e. late gadolinium enhancement) [24]. In accordance with this, we found a strong positive correlation between BNP, hs-TNT, and NYHA classes III–IV (Fig. 3). This suggests that patients with severe AS and the highest levels of BNP are highly probable, already symptomatic, and most likely with advanced symptoms. But in this subset of patients,

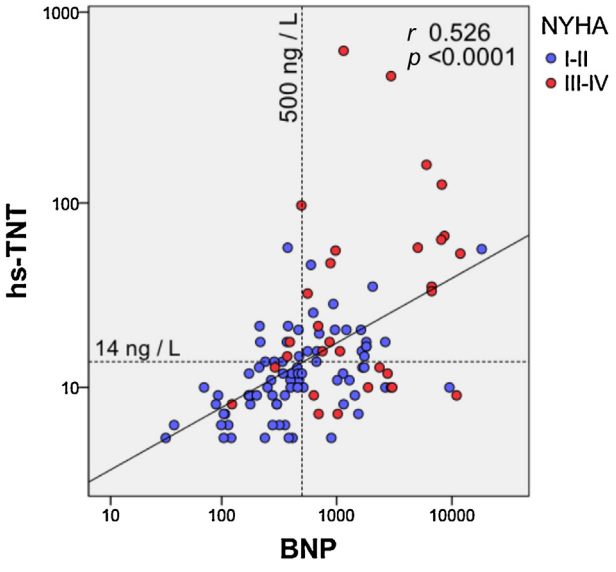

Fig. 3. Severe aortic stenosis. Correlation between BNP and hs-TNT in accordance to NYHA class. Values are represented on a logarithmic scale; *r*, Pearson correlation coefficient; BNP, B-type natriuretic peptide; hs-TNT, high-sensitive troponin T; NYHA, New York Heart Association.

myocardial damage may play a more important role in the complex pathophysiology of severe AS and heart failure symptoms on minimal exertion.

Study limitations

The vast majority of our patients underwent elective operations, which may have contributed to the relatively small number of patients with NYHA class IV symptoms. We did not separate asymptomatic from symptomatic patients in our analysis because the NYHA class I group was small and also the intention was to analyze differences between patients with or without *advanced* symptoms before AVR.

Intentionally, we did not exclude patients with coronary artery disease from analysis, with the hypothesis of possible independent contribution to LV systolic/diastolic dysfunction and thus to symptoms. Finally, our study was conducted in a single referral tertiary hospital, and therefore relatively few patients with isolated severe AS without comorbidities were included. However, our cohort may well represent the current group of patients with severe AS who are being referred for AVR.

Conclusions

Our study is the first to demonstrate that the presence of advanced symptoms in patients with severe AS referred for AVR is associated with worse intracardiac hemodynamics, absence of sinus rhythm, and with higher values of hs-TNT as a marker of myocardial damage. This supports the concept of transition from adaptive LV remodeling to myocyte death as an important determinant of symptoms of heart failure.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Zusammenfassung der Arbeit

Dissertation zur Erlangung des akademischen Grades
Dr. med.

Titel:
Advanced symptoms are associated with myocardial damage in patients with severe aortic stenosis

eingereicht von:
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angefertigt an:
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betreut von **Prof. Michael A. Borger, MD PhD**

Monat und Jahr (der Einreichung): **März 2018**

Zusammenfassung:

Calcific aortic stenosis is the most common form of valvular heart disease in the western world, growing up with the aging of the population. It represents a major healthcare burden, introducing high healthcare costs because of the associated morbidity. Nowadays, there are no medical treatments capable of delaying or halting the progression of the disease. So, the only treatment that we have available for these patients is the surgical and trans-catheter aortic valve replacement, with excellent results, which can be seen as a medical advantage of the last decades. Success, that can be attributed at least in part to a proper timing of aortic valve replacement.

Today, the proportion of patients referred for aortic valve replacement with “advanced” symptoms is still relative high. In our study population approximately 29% of patients with severe aortic stenosis were referred for aortic valve replacement presenting a NYHA class III/IV, ranging between 16 to 35% in the literature [33, 47] and being as high as 60% in

octogenarians [48]. This difference may be related or pronounced due to underestimation of symptoms in the elderly sedentary patients [49].

Now, our study shows that in patients with severe aortic stenosis referred for aortic valve replacement: (1) the presence of “advanced” symptoms at the time of admission is not associated with the severity of the aortic stenosis itself (grade of valve narrowing), but rather with age, comorbidities, worse intracardiac hemodynamics and more LV damage. Variables independently associated with NYHA III-IV symptoms are increased high sensitive-TNT, higher E/e´ ratio, and the absence of sinus rhythm; and (2) global longitudinal peak systolic strain (GLPS) showed a good correlation not only with markers of myocardial damage, but also with markers of increased afterload imposed on LV, being not independently related with the presence of “advanced” symptoms.

Interestingly, despite the protective benefits of aortic valve replacement, patients with mid-wall fibrosis (MWF) depicted by cardiovascular magnetic resonance (CMR) who undergo aortic valve replacement are still at higher risk than those without mid-wall fibrosis [50, 51]. We now demonstrate the association of advanced symptoms with myocardial damage expressed as higher levels of hs-TNT, independently of the presence of coronary artery disease. Supporting the concept of referring patients with severe aortic stenosis for aortic valve replacement in an early stage of the disease with “minimal” symptoms and “no” evidence of LV myocardial damage, avoiding the occurrence of advanced heart failure symptoms to prevent postoperative worse outcomes.

Degenerative aortic stenosis could be viewed as a disease with an initial silent phase of endothelial damage and cellular activation with consecutive valvular inflammation and lipid deposition, followed by a “propagation phase” of progressive valve sclerosis and calcification leading to a gradual development of aortic valve narrowing. In this second

phase, fibrocalcific aortic valve disease is accompanied with different grades of LV involvement: from only LV overload, through concentric LV remodeling with first compensatory hypertrophy and later also accompanied myocardial fibrosis, until advanced myocardial damage with eccentric remodeling and finally bilateral ventricle involvement [32]. In fact, once aortic stenosis is classified as severe, patients develop symptoms at different stages of the disease process. Thus, within the severe AS category, symptom status correlates poorly with the grade of valve narrowing [46]. Multiple pathophysiological mechanisms, rather than isolated valvular load, should therefore explain the link between aortic stenosis and symptom severity.

As expected, we showed that the presence of advanced symptoms was not related with the grade of valve narrowing. Contrarily, independently associated variables were worse intra-cardiac hemodynamics (i.e. higher E/e´ratio and absence of sinus rhythm) and more LV damage (i.e. higher levels of hs-TNT). It has been hypothesized, that the pathophysiology of advanced symptoms in aortic stenosis is majorly related to an imbalance between the global increase in left ventricle overload, of valvular (i.e. aortic stenosis) and/or vascular (i.e. hypertension) origin, and LV reserve [52]. Moreover, the left ventricle remodeling might not only be caused by aortic stenosis as such but also by associated comorbidities. So, in the course of disease´s progression to severe aortic stenosis the “onset” of symptoms depends on the interplay of aortic valve narrowing with multiple other linked factors, such as age, gender, and the association with comorbidities (i.e. hypertension, diabetes, coronary artery disease, etc.) which ultimately, through different levels of activation of complex paracrine and systemic signal pathways, favor or not an accelerated left ventricle remodeling with unfavorable effects like fibrosis and apoptosis leading to myocardial damage and the onset of “advanced” symptoms.

The precise mechanisms behind the transition from adaptive to maladaptive hypertrophy are poorly defined but involve cardiomyocyte death and myocardial fibrosis [40].

Summarizing, our study is the first to demonstrate that the presence of advanced symptoms in patients with severe aortic stenosis referred for aortic valve replacement is associated with worse intracardiac hemodynamics, absence of sinus rhythm, and with higher values of hs-TNT as a marker of myocardial damage. Supporting the concept of transition from adaptive LV remodeling to myocyte death as an important determinant of symptoms of heart failure and possible adverse clinical outcomes.

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Erklärung über die eigenständige Abfassung der Arbeit

Hiermit erkläre ich, dass ich die vorliegende Arbeit selbstständig und ohne unzulässige Hilfe oder Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Ich versichere, dass Dritte von mir weder unmittelbar noch mittelbar eine Vergütung oder geldwerte Leistungen für Arbeiten erhalten haben, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen, und dass die vorgelegte Arbeit weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde zum Zweck einer Promotion oder eines anderen Prüfungsverfahrens vorgelegt wurde. Alles aus anderen Quellen und von anderen Personen übernommene Material, das in der Arbeit verwendet wurde oder auf das direkt Bezug genommen wird, wurde als solches kenntlich gemacht. Insbesondere wurden alle Personen genannt, die direkt an der Entstehung der vorliegenden Arbeit beteiligt waren. Die aktuellen gesetzlichen Vorgaben in Bezug auf die Zulassung der klinischen Studien, die Bestimmungen des Tierschutzgesetzes, die Bestimmungen des Gentechnikgesetzes und die allgemeinen Datenschutzbestimmungen wurden eingehalten. Ich versichere, dass ich die Regelungen der Satzung der Universität Leipzig zur Sicherung guter wissenschaftlicher Praxis kenne und eingehalten habe.

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Datum Unterschrift

Darstellung des eigenen Beitrags

"Advanced symptoms are associated with myocardial damage in patients with severe aortic stenosis. J Cardiol. 2017 Jul;70(1):41-47".

Der wissenschaftliche Beitrag des Doktoranden zur Publikation war federführend mit einer aktiven Teilnahme an der Konzeption, Datensammlung, Literaturrecherche, Analyse der Daten und der Verfassung des Artikels.

Quantitative Beschreibung des eigenen Beitrags des Doktoranden: Konzeption 90%, Erhebung der Daten 100%, Analyse der Daten 60%, Verfassung des Artikels 90%.

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Education and training

- **1996-2002** - Medical doctor *of Medicine at National University of Cuyo – Medical School. (Universidad Nacional de Cuyo).*
- **2003-2007** - Clinical Cardiology at Cardiovascular Institute of Buenos Aires (ICBA).
- **2005-2006** - University title in Clinical Cardiology. University of Buenos Aires and Argentine Society of Cardiology.
- **2007** - Annual Course of Echocardiography. Argentine Society of Ultrasonography in Medicine and Biology (SAUMB).
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Other Experience, Certifications, and Professional Memberships

- **4-5/2001** - **Selected** to Internal Medicine Internship Rotation in Harvard Medical School, Boston – U.S.A. During April and May of 2001. **Clinical Management of Individuals with HIV Infection** (from April 30th to May 27th of 2001) and **Clinical Cardiology** (from May 28th to June 24th of 2001) in **B.I.D.M.C. Hospital, Boston – U.S.A**.
- **2011** - Medical degree in Europe – Germany ("**Approbation** als Arzt ").
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- **2016** - **ESC Level 1** Cardiovascular Magnetic Resonance (CMR) Certification. EuroCMR 2016.
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Languages

Spanish- mother language.
German- Proficient user in understanding (listening, reading), speaking and writing
English- Proficient user in understanding (listening, reading), speaking and writing

Publications and Posters

2000- “Role of Superoxide Radical in electrophysiological changes during ischemia-reperfusion process”. Spampinato R., Baiardi G., Ponce Zumino A. - Faculty of Medical Sciences, National University of Cuyo, Mendoza, Argentina.

2001- Collaborator, as Student of 6th year of Medical Sciences, in the investigation work: "Glycemic Profile at different levels of Glucosylated Hemoglobin in patients with type 2 Diabetes". Presented in the National Congress of Medicine (May of 2001) and in the Latin American Congress of Diabetes - Punta del Este – Uruguay (November of 2001).

2005- Prevalence of High Blood Pressure in a Neurology Clinic. Estol C.J., Nesa R., Spampinato R.A., et al. I.C.B.A. – 14th European Stroke Conference. Cerebrovasc Dis 2005; 19(suppl 2):1-159.

2005- Risk of Bleeding with the association of Aspirina, Clopidogrel and Oral Anticoagulation after Coronary Stenting. Aris Cancela ME, Benzadón M, Arakaki D, Turdó K, Días L, Thierer J, Spampinato R, Cortés V. ICBA, BsAs Argentina. XVII Argentine Congress of Hematology – III International Congress (III Jornadas del grupo Rioplatense Densitometría de Flujo). Nov. 2005.

2006- Comparison of the Amplitude of the P-wave from Intracardiac Electrocardiogram Obtained by Means of a Central Venous Catheter Filled with Saline Solution to That Obtained via Esophageal Electrocardiogram. M. Benzadón, D. Ortega, J Thierer, R. Spampinato Torcivia, et al. **Am J Cardiol 2006; 98: 978-981**.

2006- Outcomes of the left main coronary artery angioplasty. Spampinato Torcivia R., Albertal M., Thierer J., et al. Oral Presentation. XVIII Nationals Journeys of the Argentine Society of Cardiology. Mar del Plata, 26 y 27 del 2006.

2007- Association of Stress and elevated C Reactive Protein in patients admitted in the coronary unit. Spampinato Torcivia RA, Cohen Arazi H, Grancelli H, Nojek C, Rodríguez W, Cáceres M, et al. Oral Presentation. 23º Uruguayan Congress of Cardiology. December 2007.

2008- Cardiac papillary fibroelastoma presenting as stroke. Cover Image. Doiny D, Spampinato Torcivia RA, Caroli C, et al. **JACC. 2008; 52(7).**

2008- Surgical Treatment of Acute Type A Aortic Dissections. Immediate and Long-Term Results. World Congress of Cardiology. Buenos Aires, Argentina - **Circulation. Vol 117, 19: 62. 2008.**

2009- Should every patient who presents with a seizure have an electrocardiogram? G. Iralde, H. Arazi, S. Waldman, M. Abello, D. Doiny, R. Spampinato, M. Russo, C. Pensa, H. Grancelli. **The American Journal of Emergency Medicine, Volume 27, Issue 3, Pages 376.e3-376.e7**

2012- Pseudoaneurysm of the mitral-aortic intervalvular fibrosa as a complication after minimally invasive mitral valve repair. RA. Spampinato, MA. Borger, E Strotdrees, FW. Mohr. **Interact Cardiovasc Thorac Surg. 2013 March; 16(3): 396–398.**

2013- Relationship between severity of symptoms and markers of myocardial damage in patients with severe aortic stenosis referred to cardiac surgery. RA. Spampinato, M. Tasca, E. Strotdrees, V. Schloma, Y. Dmitrieva, M. Mende, MA. Borger, FW. Mohr. Poster. **ESC Congress 2013**.

2013- High-sensitive troponin T in patients with severe aortic stenosis referred to cardiac surgery: association with clinical and echocardiographic parameters. RA. Spampinato, M. Tasca, JG. Da Rocha E Silva, E. Strotdrees, V. Schloma, Y. Dmitrieva, M. Mende, MA. Borger, FW. Mohr. **EuroEcho-Imaging 2013**.

2014- Metabolic burden is associated with more pronounced impairment of the longitudinal strain in patients with severe aortic stenosis referred for valve surgery: 2D speckle tracking analysis. RA. Spampinato, M. Tasca, JG. Roche E Silva, E. Strotdrees, V. Schloma, Y. Dmitrieva, M. Dobrovie, MA. Borger, FW. Mohr. **EuroEcho-Imaging 2014.**

2014- Barlow´s mitral valve disease: a comparison of neochordal (Loop) and edge-to-edge (Alfieri) minimally invasive repair techniques. Rocha e Silva J.; Spampinato R.A.; Misfeld M.; Seeburger J.; Pfanmüller B.; Eifert S.; Mohr,F.W.; Borger,M.A. **Annals of thoracic surgery. 2015 Dec;100(6): 2127-33.**

2015- Aortic Annular Sizing for Transcatheter Aortic Valve Replacement: Comparison of Three Different Methods of Measurement of Effective Diameter Using Cross-Sectional Imaging (3D Trans-esophageal Echocardiography vs. Computed Tomography). RA. Spampinato, L. Lehmkuhl, M. Dobrovie, F. Thome, JG. da Rocha e Silva, V. Schloma, Y. Dmitrieva, E. Strotdrees, B. Foldyna, M. Hänsig, P. Kiefer, S.A. Leontyev, F.W. Mohr, D.M. Holzhey. Oral presentation. **Heart Valve Society 2015** Annual Scientific Meeting.

2015- Clinical and echocardiographic characteristics of patients with low flow severe aortic stenosis and preserved ejection fraction. RA. Spampinato, M. Dobrovie, JG. Da Rocha E Silva, F. Bonamigo Thome, R. Kluttig, V. Schloma, Y. Dmitrieva, E. Strotdrees, FW. Mohr. Poster**. EuroEcho-Imaging 2015.**

2016- Association between Left Ventricular Ejection Fraction, Ventricle Structural Changes and Clinical Status in Patients with Severe Aortic Stenosis referred for Surgery. R. Spampinato, M.A. Spampinato, J.G. da Rocha e Silva, V. Schloma, Y. Dmitrieva, E. Strotdrees, F-W. Mohr. Poster. **Heart Valve Society 2016** Annual Scientific Meeting.

2016- Anatomical and functional evaluation of postinterventional pulmonary vein stenosis by magnetic resonance imaging. S. Hilbert, R. Spampinato, S. Oebel, G. Hindricks, A. Bollmann, C. Jahnke, I. Paetsch. Oral Presentation (RS). **EuroCMR 2016**. Florence, Italy.

2016- Advanced symptoms are associated with myocardial damage in patients with severe aortic stenosis. Spampinato RA, Tasca M, Borger MA, Schloma V, Dmitrieva Y, Mende M, Noack T, Strotdrees E, Mohr FW. **J Cardiol. 2017 Jul;70(1):41-47.**

2016- Quantification of aortic regurgitation by pulsed Doppler examination of the left subclavian artery velocity contour: a validation study with cardiac magnetic resonance imaging. Rapid Fire Abstract (oral presentation). **EuroEcho Imaging 2016**. Leipzig, Germany. Preselected for the Highlight sessions.

2017- Artefact-free late gadolinium enhancement imaging in patients with implanted cardiac devices using a modified broadband sequence: current strategies and results from a real-world patient cohort. Hilbert S, Weber A, Nehrke K, Börnert P, Schnackenburg B, Oebel S, Spampinato R, Rogge C, Richter S, Hindricks G, Paetsch I, Jahnke C. **Europace. 2017 Apr 18**. [Epub ahead of print]

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2017- Quantification of aortic regurgitation by pulsed Doppler examination of the left subclavian artery velocity contour: a validation study with cardiac magnetic resonance imaging. Spampinato RA, Jahnke C, Paetsch I, Hilbert S, Busch F, Schloma V, Dmitrieva Y, Bonamigo Thome F, Löbe S, Strotdrees E, Hindricks G, Mohr FW, Borger MA. **J Am Soc Echocardiogr. 2018 Jan;31(1):42-51.**

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Honors

Title of General Physician conferred on Sept. 12, 2002. Final average of 9.28 – with Honors.

***Grading scale: 1 to 10 (10 is equivalent to straight A´s, or to number one -1- in Germany).**

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